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In this study the solid cancer mortality data in the Techa River Cohort in the Southern Urals region of Russia was analyzed. The cohort received protracted exposure in the 1950s due to the releases of radioactive materials from the Mayak plutonium complex. The Extended Techa River Cohort includes 29,849 people who resided along the Techa River between 1950 and 1960 and were followed from January 1, 1950 through December 31, 1999. The analysis was done within the framework of the biologically based two-stage clonal expansion (TSCE) model. It was found that about 2.6% of the 1854 solid cancer deaths (excluding 18 bone cancer cases) could be related to radiation exposure. At age 63, which is the mean age for solid cancer deaths, the excess relative risk (ERR) and excess absolute risk (EAR) were found to be 0.76 Gy^{-1} (95% CI 0.23; 1.29) and 33.0 $(10^4\ PY\ Gy)^{-1}$ (95% CI 9.8; 52.6), respectively. These risk estimates are consistent with earlier excess relative risk analyses for the same cohort. The change in the ERR with age was investigated in detail, and an increase in risk with attained age was observed. Furthermore, the data were tested for possible signs of genomic instability, and it was found that the data could be described equally well by a model incorporating effects of genomic instability. Results from the TSCE models indicated that radiation received at older ages might have stronger biological effects than exposure at younger ages.

INTRODUCTION

The Mayak Production Association, located in the Southern Urals in Russia, began operation of its first atomic reactor and radiochemical plant for plutonium separation in 1948. Large amounts of radioactive waste were released into the Techa River from 1949 to 1956 with maximal releases in 1950 and 1951. Residents along the Techa River were exposed to significant doses of protracted external and internal radiation. Starting from the 1960s, systematic collection of demographic and medical information on the exposed population and dose reconstruction have been undertaken by the staff of the Urals Research Center for Radiation Medicine (URCRM) in Chelyabinsk. Over the last decade, major improvements in the follow-up of the study population (*1*) and dosimetry (*2, 3*) have been made. A recent review of the current status of the Techa River Cohort can be found in ref. (*4*).

The Techa River Cohort provides important information on carcinogenic risks that resulted from protracted exposure in the low- and medium-dose range among an unselected population of both sexes and all ages with a follow-up time of more than 50 years. Risk assessments in the Extended Techa River Cohort (ETRC) have been performed with excess relative risk models (*5*). Based on the Techa River Dosimetry System 2000 (TRDS-2000) dose estimates, the radiation risk analysis provided strong evidence for long-term carcinogenic effects in the ETRC, and a relatively large excess risk was found.

This report presents solid cancer mortality risk assessment among the Techa River population using the two-stage clonal expansion (TSCE) model (*6, 7*). The TSCE model assumes that the key processes necessary to convert a healthy cell to a cancer cell can be reduced to two basic steps. In spite of this drastic simplification, the model has been applied successfully to various radioepidemiological data sets (*8–10*). The TSCE model can help to identify rates or time scales of basic biological processes such as the creation or growth of preneoplastic lesions. Though all identifiable parameters of the TSCE model relevant for the risk estimates can be determined from the data, the biological rates cannot be derived directly since one additional degree of freedom remains. To estimate all biological parameters, more data, e.g. on the number and size of premalignant lesions, would be needed (*11*). Since the TSCE and the excess relative risk models are based on very different descriptions of the baseline as well as the radiation risk, a comparison of the risk estimates indicates which characteristics of the risk are inherent in the data and which depend on the choice of model: If the models give very similar predictions of the risk and its behavior with age, it

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is a strong indication that these properties are contained in the data and are not a model-specific feature.

An increase of excess relative risk (ERR) with attained age was reported in ref. (*5*), and this study has investigated the behavior of risk with age in more detail. Since radiation-induced genomic instability is a topic of considerable debate in the current literature, a model incorporating this effect was applied to the data.

MATERIALS AND METHODS

The Study Cohort

For a detailed description of the radiation conditions on the Techa River and demographic characteristics of the cohort, we refer the reader to refs. (*4, 12*). The ETRC includes all people born prior to January 1, 1950 who lived at least some time during the period 1950–1960 in the 41 radioactively contaminated villages along the Techa River in the regions of Chelyabinsk and Kurgan Oblasts. The mortality follow-up begins on latest of January 1, 1950 or the date the people came to live on the Techa riverside. This research has been carried out under the approval of the URCRM institutional review board.

The study cohort used in the present report includes 29,849 individuals. About 60% of the cohort members are women. Most of the cohort members are Slavs: 20% are identified as being of Tartar or Bashkir ethnicity. About 40% of the cohort was under age 20 at the time of initial exposure, and only 30% were over age 40. The ETRC cancer mortality was followed from January 1, 1950 through December 31, 1999. The source of information on cancer death cases was death certificates (*4*). The cancer mortality catchment area included the territories of Chelyabinsk and Kurgan Oblasts, where the information on vital status and causes of deaths for exposed individuals was collected regularly. Cohort members who moved outside the borders of Chelyabinsk and Kurgan Oblasts were treated as distant migrants. At the end of the current follow-up, 14,388 cohort members had died (with cause known for 89% of deaths) and 23% were lost to follow-up mainly due to migration.

Residents of the Techa River villages received external radiation exposure mainly from contaminated river shore and flood-plain soils and internal exposure from ingestion of radionuclides (^{137}Cs, ^{90}Sr, ^{89}Sr and short-lived radionuclides) with drinking water and local foodstuffs. The dose estimates were computed by the URCRM dosimetry team using the Techa River Dosimetry System 2000 (TRDS-2000) (*2, 3, 13*). The TRDS-2000 provides annual dose estimates for each individual in the cohort starting from January 1, 1950 or date of arrival in the Techa River area through the end of follow-up, i.e. December 31, 1999, date of death, or date of migration from the catchment area. Dose estimates were computed taking into account age-dependent parameters of internal and external exposures, detailed information on residency on the contaminated area, and the date of last known vital status. However, neither the precise locations of individual residences within villages nor detailed lifestyle patterns were taken into consideration. For the ETRC members, places and periods of residence during the follow-up time are known with an indicator whether the residence is inside or outside the cancer mortality catchment area. The cohort members were not considered to be at risk when they were known to reside outside the catchment area or when their places of residence were unknown because they were not under active follow-up in such periods. The cohort has a total of 867,238 person years at risk.

In this study we have analyzed the deaths from solid cancer (ICD-9 codes 140–199) other than bone cancer (ICD-9 code 170). The doses received by ^{90}Sr show only a small correlation to the doses from ^{137}Cs. Since strontium accumulates in the bones, it can lead to bone doses of several grays with large uncertainties. To avoid this additional source of uncertainty and a potential bias from the ^{90}Sr doses, we have excluded bone cancers from the analyses. In total, 1854 solid cancer deaths (excluding bone cancer deaths) occurred between 1950 and 1999. The distributions of person years and cancer deaths as a function of age are presented in Fig. 1. The solid cancer risk analysis is based on stomach dose. This choice was made because stomach dose is similar to absorbed doses in the lung and other soft tissues. In addition, stomach cancer is the most common cause of cancer death. On average, about 75% of the dose to the stomach is due to external exposure while the remainder is a result of the ingestion of radiocesium. Stomach dose estimates range up to 0.48 Gy with a mean of 0.03 Gy. The cumulative stomach doses are essentially unchanged after 1960.

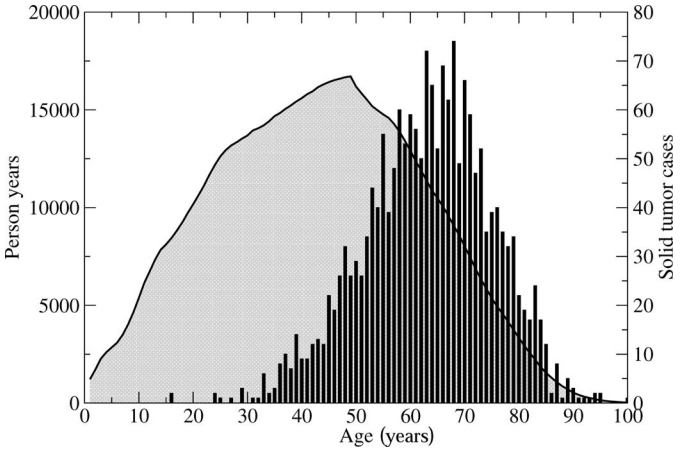

FIG. 1. Distribution of person years (gray area) and solid cancer cases (bars) as a function of age.

The analysis was performed for all solid cancer types together since the number of excess cases is large enough to obtain significant risk estimates and investigate the behavior of risk with age. However, since it is known that lung cancer may show a different age dependence than other cancers and since lung cancer risk could be biased by smoking, we also performed an analysis for all solid cancers excluding lung cancer. In this study we have not included an analysis of individual cancer sites since the number of excess cases is small (about 12 cases for stomach and less than 10 cases for other cancer sites) so that it is difficult to obtain significant risk estimates and the statistical power is too low to make predictions about the changes of risk with age.

TSCE Model for Carcinogenesis

In the TSCE model (Fig. 2), it is assumed that the complex process leading to cancer can be reduced to two basic steps. In the first step, called initiation, a healthy cell may experience several mutations that will result in an intermediate cell. This process occurs with effective initiation rate $\nu(t)$, where t is the age of the person. The intermediate cells divide with rate $\alpha(t)$ and differentiate or are inactivated at rate $\beta(t)$. A primary intermediate cell together with its daughter cells forms a clone of intermediate cells. The process of clonal growth of intermediate cells is called promotion. In a second step, these intermediate cells mutate with the transformation rate $\mu(t)$ to malignant cells. Once a malignant cell is produced, it is assumed to lead within a given lag time t_{lag} to death. We have tested different lag times, but the lag time was found not to have a major influence on the results. Thus we have chosen $t_{lag} = 5$ years (*14*), and this value will be used in the rest of this work. Preliminary analyses have shown that a time or dose dependence of the transformation rate does not improve the description of the data. Under the assumption of a time-independent transformation rate, the hazard can be described in terms of three parameters:

$$X = N_s \cdot \mu \cdot \nu;$$

$$\gamma = \alpha - \beta - \mu;$$

$$q = \frac{1}{2}\left(\sqrt{\gamma^2 + 4\alpha\mu} - \gamma\right); \quad (1)$$

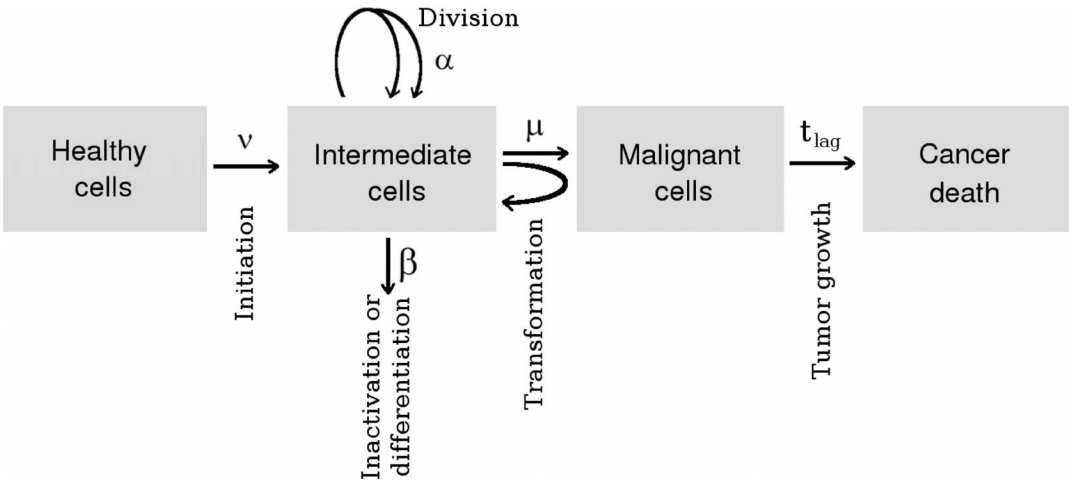

FIG. 2. TSCE model.

N_s is the number of healthy stem cells. To describe the spontaneous cancer risk, we have used constant values of these parameters over lifetime. It is important to note that even for constant parameters the model predicts an increasing hazard function with age: The number and size of intermediate clones grows over time, and thus the probability of a malignant transformation will increase. The parameter X is the slope of the hazard function at young ages, γ represents the promotion rate of intermediate cells for medium ages. The parameter q determines the asymptotic value X/q of the hazard for older ages. The value of q is also an upper bound for the transformation rate μ (*15*).

Significant baseline corrections are given by gender, birth-year, ethnic and oblast adjustments, and the baseline is parameterized by

$$\begin{aligned} X_{base} &= X_p; \\ \gamma_{base} &= \gamma_p + byr_p \cdot (\text{birth year} - 1925); \\ q_{base} &= q_p + kur \cdot \text{oblast} + tar \cdot \text{ethn}; \end{aligned} \tag{2}$$

$P = m/f$ for males or females, oblast is zero for residents of Chelyabinsk Oblast and one for Kurgan Oblast residents; ethn is zero for Slavs and one for Tartars and Bashkirs. Since the solid cancer mortality baseline risk for males and females differs significantly, we have taken a separate set of parameters X, γ and q for each gender. The best description of the data is found when γ depends on birth year and q depends on oblast and ethnicity. Furthermore, the birth-year effect is different for males and females. Thus we have included 10 baseline parameters in the model.

The effects of radiation exposure can be incorporated in the model by allowing for a change in the parameters with the dose rate. As will be shown in the Results section, the exposure risk is described best with the radiation acting linearly on the initiation rate, whereas there is little evidence for an action of radiation on promotion or transformation. In the most simple description, the initiation rate is thus parameterized as

$$X(t) = X_{base}[1 + d(t) \cdot X_1], \tag{3}$$

where $d(t)$ represents the dose rate of a specific person at age t. To allow for an age dependence of the radiation effect, we have chosen the following dependence in the ''main'' TSCE model that will be used for the risk estimates:

$$X(t) = \begin{cases} X_{base}[1 + d(t) \cdot X_1]: & t < a_{\text{tr}} \\ X_{base}[1 + d(t) \cdot X_2]: & t > a_{\text{tr}}, \end{cases} \tag{4}$$

where a_{tr} is an age of transition between different periods of radiation sensitivity.

The dose rate is given in form of annual dose values. The model parameters are assumed to be constant within each calendar year. For piecewise constant parameters, the TSCE model can be solved stepwise analytically (*16*) and the hazard $h(t)$ can be determined. The total likelihood L_{tot} is then obtained from the product of the likelihoods of all cohort members $L_{tot} = \Pi_i L_i(\Psi_i, t_{1i}, t_{2i})$ (*9*), where Ψ_i is the survival function for the exposure history of person i and t_{1i} and t_{2i} are the ages at beginning and end of follow-up. This method does not group data, but it takes into account the individual exposure history of each person. To determine the best values of the parameters, we have performed a maximum likelihood (minimum deviance) fit of all parameters simultaneously using the program MINUIT from the CERN library (*17*). The best fit of the parameters is obtained by minimizing the deviance

$$\text{Dev} = -2 \ln L_{tot}. \tag{5}$$

Once the parameters have been obtained, the excess relative risk (ERR) and excess absolute risk (EAR) per unit dose for each person at age t can be computed as

$$\begin{aligned} \text{ERR}_i(t) &= [h_i(t)/h_{base,i}(t) - 1]/D_i(t - t_{lag}); \\ \text{EAR}_i(t) &= [h_i(t) - h_{base,i}(t)]/D_i(t - t_{lag}); \end{aligned} \tag{6}$$

$D_i(t - t_{lag})$ is the total accumulated dose at $t - t_{lag}$; the hazard $h_i(t)$ depends on the exposure history of person i and thus can be different for two persons with the same age and the same accumulated dose. The ERR(t) and EAR(t) for the total cohort at a certain age t can then be obtained by averaging over the person risks.

For an estimate of the uncertainty bounds, we have simulated 10,000 Monte Carlo realizations from the parameter distributions. Since the uncertainties of the parameters turn out to be distributed almost symmetrically, we have assumed a usual Gauss distribution. In a computer program written by one of us (ME), we have created these realizations taking into account the correlation matrix of the parameters given by MINUIT within a distribution-free approach (*18*) and using Latin Hypercube Sampling (*19*). We have checked the program for the correct distributions and correlations and compared them to the results from Crystal Ball (*20*) as a double check. For each realization the baseline risk, ERR(t) and EAR(t) of the cohort can be calculated for each age t. The values of the percentiles of the full set of realizations then provide the uncertainty bounds.

For the comparison of the TSCE model to the empirical ERR model, the ERR model described in ref. (*5*) was used. We have redone the analysis with a maximum likelihood fit based on individual data and with grouped data using EPICURE (*21*). The results turned out to be almost equal and, unless otherwise specified, we have presented the results from the EPICURE analysis. For the main analysis, we have used a log-linear model with attained age as radiation effect modifier where the ERR is parameterized by $D \cdot \alpha \cdot \exp(\beta \cdot \ln a_{att}/70)$, where D is the time-lagged accumulated dose, a_{att} is attained age, and α and β are fit parameters. To see whether an age-at-exposure effect can be seen in addition to the

attained-age modifier, we have also investigated a model where the ERR is given as $D\cdot(\alpha\cdot\exp(\beta\cdot\ln a_{att}/70) + \Delta\mathrm{ERR}_{exp}\cdot\Theta(a_{exp} - a_{exp,0}))$, where a_{exp} is age at exposure, Θ is 1 if $a_{exp} > a_{exp,0}$ and 0 otherwise, and $\Delta\mathrm{ERR}_{exp}$ gives the change in ERR due to the age at exposure after $a_{exp,0}$, with $\Delta\mathrm{ERR}_{exp}$ and $a_{exp,0}$ as fit parameters.

Models of Genomic Instability

Radiation may induce changes in cells that seem to have no effect immediately after exposure but do induce genomic alterations after several or many cell generations. Such radiation-induced genomic instability (*22*) could modify the rate of mutations necessary for the development of cancer. In principle, genomic instability could appear at any stage in the carcinogenic process. Since the TSCE model is described by biological parameters, it is possible to investigate potential consequences of genomic instability. We assume that the appearance of radiation-induced genomic instability will effectively increase the rate at which initiation, promotion or transformation occurs, and this increase will take place not only during the radiation exposure but also at a later time. Many variations are possible; e.g., mutations could show up directly after exposure or with a certain lag time, doses received more recently could have a stronger effect than doses received longer time ago, or the mutations may need an activation dose to appear. The outcomes of such a model testing should be interpreted with caution since positive or negative results do not (dis)prove genomic instability but rather could only indicate whether the data are consistent with the genomic instability hypothesis.

We have analyzed different variations of the TSCE model by using a standard radiation action on initiation, $X(t) = X_{base}(1 + d(t)\cdot X_1)$, and then incorporating the above-mentioned effects. Some of the tested models are presented in Fig. 3. The y axis shows the changes in the initiation rate per dose (with arbitrary scale), due to a dose received at some age t_0, as a function of time since exposure. The first panel shows a model of genomic instability in which a dose received at t_0 leads to a constantly increased X over the lifetime; i.e., cellular abnormalities will remain forever and lead to an increased production of intermediate cells. Panels 2 and 3 show models where the increase stops or starts after some time, respectively. The last panel shows an exponentially decreasing effect of genomic instability with time where the cellular abnormalities are ''dying out''.

With one exception, we have found that none of the models gives a significantly better description than the TSCE model without genomic instability. The only model with a significant improvement is similar to the first graph, but with the assumption that genomic instability has an effect only if radiation exposure took place after a certain age. At some age t, the initiation rate can then be described as

$$X(t) = X_{base}\left[1 + d(t)\cdot X_1 + X_2\cdot\int_{a_{tr}}^{t} d(t')\,dt'\right], \qquad (7)$$

where the term $\propto X_2$ is zero for $t < a_{tr}$; i.e., all doses received after a_{tr} will lead to an increase in the initiation rate over lifetime and the increase at age t is proportional to the accumulated dose between a_{tr} and t. Thus X_2 has a different meaning than the same parameter in Eq. (4), where it described an increase of the initiation rate only during the action of radiation.

RESULTS

Model Choice and Baseline Results

In Table 1 we compare different models by deviance and number of parameters; all deviances are calculated from a maximum individual likelihood fit. All models have 10 baseline parameters, and the additional parameters are used to describe the radiation effect. The first line presents the result from the simple linear TSCE model of Eq. (3) with just one additional parameter, X_1. Compared to the baseline without a radiation modifier with a deviance of 23866.2, the model has one more parameter, and the radiation risk is significant at the 95% level ($P = 0.02$) (*23*). A radiation action on promotion or transformation, on the other hand, does not give a significant radiation effect, $P = 0.29$ and $P = 0.34$, respectively. Inclusion of a radiation action on promotion, in addition to an action on initiation, does not improve the fit. We have also tested a linear-quadratic model. The quadratic term gives no improvement to the simple linear model ($P = 0.75$), and we conclude that we have no indication for a quadratic dose response in the Techa River Cohort as was already found with the empirical ERR model in ref. (*5*). The next model assumes an additional linear dependence of the initiation rate with attained age, which already improves the fit substantially. The next two entries present the results for the best TSCE model of Eq. (4) and the TSCE model with genomic instability from Eq. (7); the deviance of both models is very similar. Compared to the simple TSCE model, the quality of fit is significantly improved ($P = 0.004$ and $P = 0.006$, respectively), and the radiation effect in different dose categories is described much better.

The ERR model of ref. (*5*) was reproduced to give the central radiation risk estimate. As will be discussed below, the higher deviance of this model compared to the TSCE models is largely due to a different shape of the hazard as a function of attained age. To check whether a change in the ERR with attained age can be seen in empirical models, we have tested a linear model where the ERR is parameterized by $D\cdot(r_1 + r_2(a_{att} - 63))$ with best-fit parameters of $r_1 = 0.884\ \mathrm{Gy}^{-1}$ and $r_2 = 0.075\ (\mathrm{Gy\ year})^{-1}$, where D is the time-lagged accumulated dose, a_{att} is attained age, and 63 is the mean age of all solid cancer deaths. For the log-linear model with attained age as radiation effect modifier, where the ERR is parameterized by $D\cdot\alpha\cdot\exp(\beta\cdot\ln a_{att}/70)$, we obtain values of $\alpha = 1.3\ \mathrm{Gy}^{-1}$ and $\beta = 3.2$. The deviances are given in Table 1; it can be seen that an increase in ERR with attained age also improves the description of the empirical models significantly.

When investigating the change of ERR with age at exposure, one must be careful not to mix the age-at-exposure effect with an attained-age effect since the two effects are correlated. For example, an investigation of an age-at-exposure effect without an attained-age modifier finds an (insignificant) increase in ERR with age at exposure; however, this effect vanishes when an attained-age modifier is included. Nevertheless, an age-at-exposure effect can still be seen: Including an age-at-exposure modifier as presented in the last section, we find $\Delta\mathrm{ERR}_{exp} = 1.20\ \mathrm{Gy}^{-1}$ and $\alpha_{exp,0} = 30$ years with $\alpha = 0.47\ \mathrm{Gy}^{-1}$ and $\beta = 3.96$. Thus the ERR is substantially larger for the people exposed after the age of 30 years than before. However, this effect is not significant: Compared to the log-linear attained age model without an age at exposure modifier, the deviance decreases by 2.1 points for two more parameters ($P = 0.35$), so we will

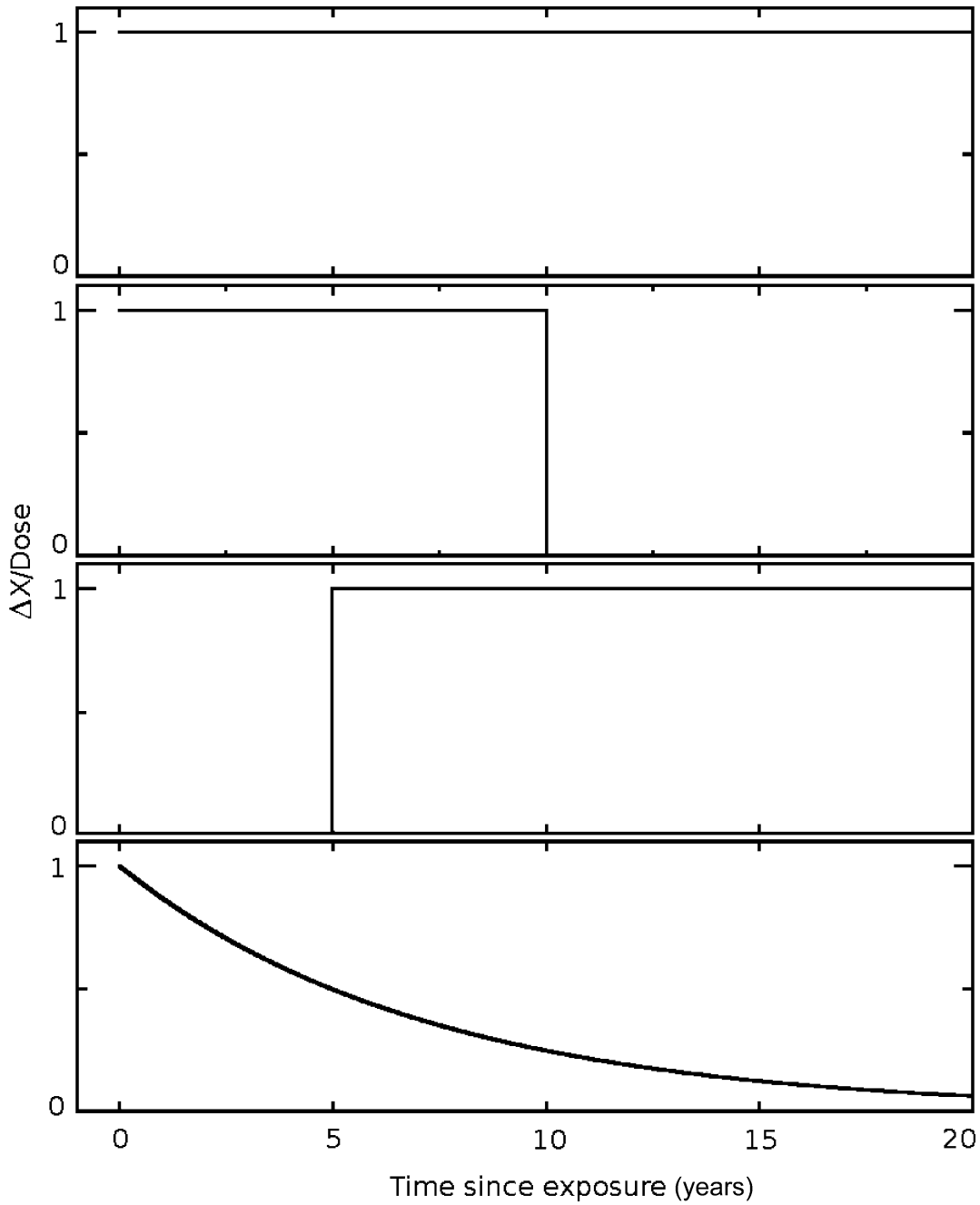

FIG. 3. Some models for genomic instability. The effect of dose received at age t_0 leads to an increase in the initiation rate at later times; the scale is arbitrary. See the text for the discussion of the models.

use the log-linear attained age model without an age-at-exposure modifier as our main ERR model in the rest of this work.

The best-fit values for the main TSCE model of Eq. (4) with the 1σ range are shown in Table 2.

Most of the errors are typically about 30–40%, with a good precision of the promotion rate $\gamma_{m/f}$ (below 10%) and the largest uncertainty in byr_m (almost twice its value). The radiation exposure risk for older attained ages (age $\geq$ 60 years) is determined mainly by the parameter X_2.

As found in other populations, the baseline risk for men is substantially (a factor of two to three) higher than that for women after middle ages. The birth-year effect is also different for both sexes. It was shown that Slavs have higher risk compared to Tartars/Bashkirs that can be explained by differences in lifestyle habits and possibly by different genetic backgrounds. Residents of Kurgan Oblast have lower solid cancer mortality rates compared to the inhabitants of Chelyabinsk Oblast. As of now the reasons for lower solid cancer death rates in Kurgan Oblast are not clear and need further investigation, but this difference cannot be explained by a difference in the probability to determine the

TABLE 1
Comparison of Different TSCE and Empirical ERR Models

	No. of fitted parameters	Deviance	*P* value
TSCE models			
Initiation simple (Eq. 3)	11	23860.9	
Promotion	11	23865.1	
Transformation	11	23865.3	
Initiation + promotion	12	23860.9	1.0
Initiation simple + quadratic in dose	12	23860.8	0.75
Initiation simple + linear in attained age	12	23857.4	0.06
Initiation main model (Eq. 4)	13	23849.9	0.004
Initiation with genomic instability (Eq. 7)	13	23850.7	0.006
Empirical ERR models			
Constant ERR as in ref. (*5*)	11	23903.3	
ERR constant + linear in attained age	12	23896.7	0.01
ERR log-linear with attained age as modifier	12	23898.6	0.03
ERR log-linear in attained age + age at exposure modifier	14	23896.5	0.08

Notes. All models have 10 baseline parameters. The *P* values are given with respect to the simple initiation model (Eq. 3) for the TSCE models and to the constant ERR model for the empirical models.

cause of death (*5*). The change of the hazard function with these baseline risk factors is very similar in direction and magnitude in both the TSCE and ERR models and is in accordance with the findings of ref. (*5*); we refer the reader to that paper for a more detailed discussion on these risk factors.

Radiation Exposure Risk for Solid Tumors

We first discuss the analysis of all solid cancers with the main TSCE model; in the following section we will present the results of the model including genomic instability. Tables 3 and 4 show the predicted and observed distribution of cancer cases by dose and attained-age categories, respectively. For a better comparison, we have also included the results from the ERR model. Classified by dose categories, the baseline and model predictions of the two different models are very similar. Both models predict almost the same number of excess cases. The differences in the models in the baseline cases are small compared to the total of 1805 baseline cases and are probably of statistical origin. The results based on the TSCE model fit indicate that 49 of 1854 solid cancer deaths are possibly associated with radiation exposure, corresponding to 2.6% of all cancer deaths. Since the value of X_2 is significantly larger than X_1 (Table 2), the TSCE model predicts a significant dose-dependent increase in the initiation rate $X(t)$ with age at exposure.

In Figs. 4 and 5 we have plotted the ERR and EAR as a function of attained age. The solid line with the error bars shows the results for the main TSCE model. More than 80% of the cancer cases occurred between 45 and 80 years (see Fig. 1). Thus the hazard is well known in this age range, and we expect the models to give a reliable risk description in the ETRC for these ages. For younger and older ages, the risk estimates will be increasingly dependent on the model. The ERR shows an unusual variation with age: It remains relatively constant until the age of 60–65 years; after the age of 65, the ERR starts to increase about twofold compared with those who are under 65. Though the specific form of this increase is dependent on the model, the increase itself is a property that can be seen in all models fitted to the ETRC data. For clarity, we have only given the error bars for the main TSCE model, but the uncertainty ranges of the other models are similar. For ages below 55

TABLE 2
Best Fit and 1 σ Errors of the Parameters from the Maximum Likelihood Analysis of the Main TSCE Model (Eq. 4)

Parameter	Value	Error
X_m/X_f (year^{-2})	$5.3 \times 10^{-7}/9.7 \times 10^{-7}$	$\pm 2.0 \times 10^{-7}/\pm 3.3 \times 10^{-7}$
γ_m/γ_f (year^{-1})	0.15/0.12	$\pm 0.010/\pm 0.0095$
q_m/q_f (year^{-1})	$3.1 \times 10^{-5}/1.7 \times 10^{-4}$	$\pm 1.1 \times 10^{-5}/\pm 6.0 \times 10^{-5}$
bry_m/bry_f (year^{-2})	$-7.1 \times 10^{-5}/-5.4 \times 10^{-4}$	$\pm 1.4 \times 10^{-4}/\pm 1.7 \times 10^{-4}$
kur (year^{-1})	3.2×10^{-5}	$\pm 1.5 \times 10^{-5}$
tar (year^{-1})	2.5×10^{-5}	$\pm 1.1 \times 10^{-5}$
a_{tr} (year)	28.53	± 0.02
X_1/X_2 (year Gy^{-1})	28.9/403.1	$\pm 25.1/\pm 132.4$

TABLE 3
Number of Baseline, Observed and Predicted Solid Cancer Deaths Based on the Main TSCE (Eq. 4) and Empirical Log-Linear ERR Models by 5-Year Time-Lagged Dose Categories

		Number of solid cancer deaths				
		Baseline prediction		Model prediction		
Dose (mGy)	Person years	TSCE	ERR	TSCE	ERR	Observed
<10	631,378	1300.4	1287.7	1305.4	1292.4	1294
10–50	158,533	336.3	344.0	345.8	352.5	350
50–100	19,257	37.4	38.0	39.7	40.5	40
100–200	29,848	63.7	65.5	72.7	74.1	73
200–300	8,719	15.2	15.6	19.3	19.6	24
300–500	19,503	51.9	53.5	71.1	74.8	73
Total	867,238	1805	1804	1854	1854	1854

years, the 95% confidence intervals of ERR and EAR estimates include zero, but for older ages, the lower bounds of the confidence intervals for both risk estimates are significantly above zero. In Fig. 4 it can be seen that the smallest error bounds for the ERR are in the range between 55 and 70 years, where most of the cancer cases also occurred. Since changes in the baseline might modify the risk estimates, we have computed the correlations between the baseline and the dose parameters. The magnitude of the correlation coefficients remains below 0.2, indicating that changes in the baseline will have only a small effect on the dose–response function and the risks obtained.

Table 5 presents predictions of the ERR and EAR based on the different models. Because causes of death are unknown for about 11% of the deceased cohort members, the EAR estimate is biased downward. Assuming that the distribution of causes of death among deceased individuals with unknown cause is similar to that seen in those with known cause, the EAR estimate is likely to be about 11% too low. Using the empirical ERR model as in ref. (*5*), but with individual maximum likelihood analysis, we obtain a central ERR of 0.91 Gy^{-1} (95% CI 0.16; 1.65). This estimate agrees almost exactly with the result published in ref. (*5*), where an ERR of 0.92 Gy^{-1} (95% CI 0.2; 1.7) was obtained using grouped data and Poisson regression with the program EPICURE.

At the age of 63 years, which is the mean age for all solid cancer deaths, the TSCE model gives an ERR(63 years) = 0.76 Gy^{-1} (95% CI 0.23; 1.29), which is slightly lower than the central ERR estimate but agrees well within the errors. For the excess absolute risk we obtain an EAR(63 years) of 33.0 $(10^4$ PY $Gy)^{-1}$ (95% CI 9.8; 52.6). From Table 5 it can be seen that the EAR estimates of both models agree well within the confidence intervals.

Table 1 shows the deviances of different models; it turns out that the deviances of the TSCE models are lower by about 40–50 points than those of the ERR models with the same number of parameters. The reason can be understood by looking at the hazard as a function of age. From Table 4 we see that, in the age range between 40 and 60 years, the ERR model predicts a hazard that is somewhat higher than the actual death rate, and in the range of 60–80 years it turns out to be lower. In both age ranges the TSCE model better reproduces the specific form of the actual death rates.

Since the hazard of lung cancer shows a different age dependence than other cancers, we have also redone the analysis of the ETRC solid cancer mortality using the TSCE model of Eq. (4) and excluding lung cancer deaths. The excess relative risk with an ERR(63 years) is 0.75 Gy^{-1} (95% CI 0.21; 1.32) for solid cancers excluding lung cancer, and its dependence on attained age was found to be almost identical to the risk for all solid cancers; only the

TABLE 4
Number of Baseline, Observed and Predicted Solid Cancer Deaths Based on the Main TSCE (Eq. 4) and Empirical Log-Linear ERR Models by Attained Age Categories

		Number of solid cancer deaths				
		Baseline prediction		Model prediction		
Age attained	Person years	TSCE	ERR	TSCE	ERR	Observed
<40	356,328	52.5	47.4	53.6	48.6	61
40–50	161,757	170.2	201.7	173.5	207.8	180
50–60	152,756	441.5	449.4	448.7	462.7	428
60–70	112,373	593.3	546.4	605.3	560.7	608
70–80	61,150	397.0	388.6	413.0	398.2	439
>80	22,874	150.4	170.8	159.8	176.0	138
Total	867,238	1805	1804	1854	1854	1854

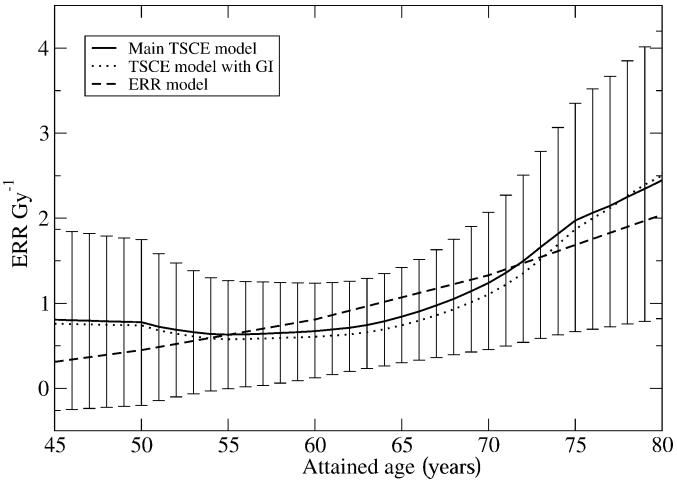

FIG. 4. ERR per dose as a function of attained age with the 95% CI. For clarity, the error bars are shown only for the main TSCE model (solid line); the uncertainties of the other models are of similar size.

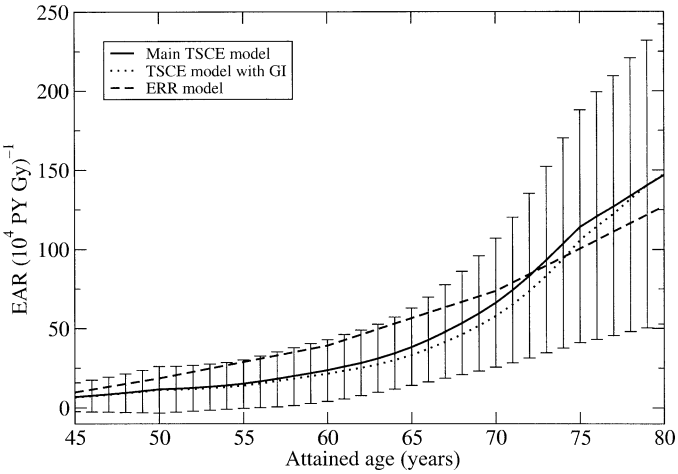

FIG. 5. EAR per dose as a function of attained age with the 95% CI. For clarity, the error bars are shown only for the main TSCE model (solid line); the uncertainties of the other models are of similar size.

value of the excess absolute risk with an EAR(63 years) of 27.3 (10^4 PY Gy)$^{-1}$ (95% CI 7.9; 45.6) was reduced by about 17% due to the fewer number of cancer cases. The error bounds were slightly larger and the ERR was significantly different from zero at the 95% CI level for ages of 56 years and over.

Genomic Instability

The best estimate of the TSCE model with genomic instability from Eq. (7) gives a transition age of $a_{tr} = 29.4$ years; thus only after this age could radiation-induced cell abnormalities appear. For the other two parameters, we obtain $X_1 = 30.9 \pm 25.3$ years Gy^{-1} and $X_2 = 42.0 \pm 16.0$ Gy^{-1}. The deviance of 23850.7 is close to the main TSCE model of Eq. (4). Figures 4 and 5 show the ERR and EAR as a function of age. Similar to the main TSCE model, the TSCE model with genomic instability predicts an increase in the ERR with attained age, and in spite of the large error bounds the risk estimates are very close. Table 5 presents the point risk estimates together with their error bounds. The ERR and EAR estimates at age 63, the mean age of death from all solid cancers, excluding bone cancers, are equal to 0.67 Gy^{-1} (95% CI 0.18; 1.18) and 28.7 (10^4 PY Gy)$^{-1}$ (95% CI 7.0; 48.1), respectively. The transition age is very close to the corresponding transition age in the main TSCE model from Eq. (4). Since the deviances of the TSCE models with and without genomic instability are similar, there is no strong preference for either model. However, the main model predicts that for older ages an annual dose of 2.5 mGy doubles the spontaneous initiation rate. Such low doubling doses are not known from radiobiological observations. This gives a preference to the TSCE model with radiation-induced genomic instability, in which such a low doubling dose does not occur.

DISCUSSION

The Techa River Cohort has specific features that make it especially valuable for radiation risk assessments and protection standards: It consists of a large, unselected population of men and women of all ages with a long follow-up time of 50 years. The doses were received over a period

TABLE 5
Predictions of Maximum Likelihood Analyses Based on the Main TSCE Model, Empirical Log-Linear ERR Model and the TSCE Model with Genomic Instability

	TSCE model	ERR model	TSCE with genomic instability
ERR (50 years)	0.78 (−0.20; 1.75)	0.45 (0.17; 0.78)	0.74 (−0.24; 1.73)
ERR (60 years)	0.68 (0.12; 1.24)	0.81 (0.30; 1.41)	0.61 (0.07; 1.16)
ERR (70 years)	1.27 (0.46; 2.07)	1.33 (0.49; 2.31)	1.13 (0.39; 1.88)
ERR (80 years)	2.53 (0.82; 4.20)	2.04 (0.75; 3.55)	2.59 (0.77; 4.40)
EAR (50 years)	12.5 (−3.3; 26.1)	18.6 (7.0; 30.8)	11.9 (−4.1; 26.1)
EAR (60 years)	25.2 (4.0; 43.0)	39.2 (14.7; 65.0)	22.4 (2.1; 40.2)
EAR (70 years)	70.1 (25.6; 107.0)	73.7 (27.6; 122.3)	60.5 (21.8; 95.0)
EAR (80 years)	155.2 (52.7; 242.2)	127.3 (47.7; 211.3)	154.8 (48.6; 249.5)

Note. The ERR and EAR for different attained ages are shown with the 95% CI in units of Gy^{-1} and (10^4 PY Gy)$^{-1}$, respectively.

of several years with cumulative doses in the low to medium range. The ETRC is still under active investigation, and in this study we used data on solid cancer mortality follow-up from January 1, 1950 through December 31, 1999 with the dose estimates based on TRDS-2000. The cohort has several limitations: 23% of the cohort is lost to follow-up. This could be a potential bias for the risk estimates if these people had a different exposure pattern. However, there are no indications that this might be the case. Furthermore, the doses have been determined without taking the precise location of individual residences within villages or detailed lifestyle patterns into account. A new dosimetry system is expected in 2008 that will address these issues, and it will be important to see whether the new dosimetry system will result in substantial changes in the risk estimates.

The results of the analysis presented in this report complement those obtained by Krestinina *et al.* (*5*) but also extend them in several respects. The variation of excess risk with age has been discussed in detail as well as we have tested models with genomic instability. The direct comparison of the TSCE and the empirical ERR models gives important insights to the model dependence of the results: It is found that both analyses agree in their central risk estimates. In both models the same type and number of baseline parameters are important, and the influence of the parameters on the hazard function has the same direction and magnitude even though these baseline parameters are implemented in a very different way. Both models show a significant increase of solid cancer mortality due to radiation exposure with a linear dependence of risk on dose. In the study of Krestinina *et al.* (*5*) a central risk estimate of an ERR of 0.92 Gy^{-1} (95% CI 0.2; 1.7) was given. The TSCE model predicts a risk that remains relatively constant until an age of about 65 years in a range of $0.65\ Gy^{-1} < ERR < 0.85\ Gy^{-1}$ (see Fig. 4). For older ages the risk increases more than two times compared to the risk estimates for younger ages. The central risk estimate obtained from the ERR model lies in between these two ranges.

Since the uncertainty bounds are relatively large, one could question the significance of the increase in ERR with age. However, the investigation of genomic instability not only gives a different interpretation but also allows testing of a different risk model. Though we have tested different models of genomic instability that resulted in very different age dependences of the risk, we found that the best model gives risk estimates very similar to that of the main TSCE model. It could be argued that, in the presence of correlations between the baseline and risk parameters, the similar baseline of both TSCE models might influence this finding. However, even in the log-linear ERR model with a completely different parameterization of the baseline and the radiation action, the increase in risk with age is similar to that predicted by the TSCE models. Though it can be seen from Table 4 that there is some difference in the baseline description, Tables 3 and 5 and Fig. 4 show that in spite of the large uncertainties, the radiation risk estimates of all the models are in very good agreement. This gives strong support to the notion that the increase in risk with attained age is a property of the data rather than a model-specific feature.

One should be careful to relate the parameter values obtained with the TSCE models to actual biological processes. Cancer sites might differ in biological mechanisms and could have different numbers of stages or a different dose response. Thus the results should only be interpreted as average values for all solid cancers and should not be transferred directly to individual cancer sites. Furthermore, as discussed in ref. (*11*), different models could fit the data equally well. Based on the deviance, it is not possible to distinguish between the main TSCE model of Eq. (4) and the TSCE model including genomic instability of Eq. (7) although they represent very different mechanisms. On the other hand, there is a good indication that radiation acts on an early stage of carcinogenesis because models with a radiation action on promotion or transformation alone fitted the data significantly less well and because adding such mechanisms to an action on the initiation rate does not improve the fits.

Though the TSCE model has been applied successfully to various radioepidemiological data sets (*8–10*), a limitation of this model is its restriction to two-stage processes. A three-stage (or many-stage) clonal expansion model might be better for some cancer sites. However, the number of parameters in these models is substantially larger than in the TSCE model, and it will be very difficult to determine all the parameters from the data set alone. Without knowledge of some of the parameters, it would be necessary to make assumptions about some transition rates, again limiting the value of these models. Though this is certainly a direction for future research, much work remains to be done, and it is not clear whether these models could better relate the data to biological processes without more input from e.g. data sets with high statistical power.

The variation of the initiation rate with age was also investigated by Kai *et al.* (*8*), who applied the TSCE model to obtain risk estimates for site-specific cancers in the atomic bomb survivors. It was found that for female lung cancer a dose-dependent increase of the initiation rate with age at exposure was significant, as we found in this work for all solid cancers together. However, it may be noted that Kai *et al.* did not find evidence of an age-at-exposure dependence for lung cancer among males or for stomach and colon.

To compare the risk estimates for the atomic bomb survivors with those for the ETRC members, we have calculated the risk from Preston *et al.* (*24, 25*) with age at exposure of 28 years and an attained age of 63 years, which correspond to the mean age of the Techa River population in 1950 and the mean age of solid cancer death. For the A-bomb survivors, this gives estimates of an ERR of 0.49 Gy^{-1} (95% CI 0.39; 0.60) and an EAR of 19.6 (10^4 PY

Gy)$^{-1}$ (95% CI 15.4; 23.7).[2] Comparing these values to those from the TSCE model for the Techa River Cohort, an ERR(63 years) of 0.76 Gy^{-1} (95% CI 0.23; 1.29) and an EAR(63 years) of 33.0 (10^4 PY Gy)$^{-1}$ (95% CI 9.8; 52.6), we see that though both risk estimates in the ETRC are larger than the risk for the A-bomb survivors, their 95% confidence intervals are overlapping. The difference is not likely to be caused by a difference in total cumulative dose. Taking into account only persons from the LSS cohort with doses less than 500 mSv, the ERR goes down by about 10%. For older ages the discrepancy grows since the TSCE model predicts an increasing risk with age. At age about 70 years, the risk of the A-bomb survivors is at the lower bound of the 95% CI. However, in a new analysis of solid cancer incidence data (*26*), the ERR as function of age at exposure was also fitted with non-parametric models and with log-quadratic splines. In these models an increase in ERR is seen for the 60+ age-at-exposure group. The standardized, gender-averaged ERR and EAR estimates for those exposed late in life were found to be comparable to those for the youngest survivors and considerably greater than those for people exposed as young adults. The error bounds of the estimates for the Techa River Cohort will be wider when taking the possible uncertainties in the dose estimates into account. Therefore, a comparison of the two cohorts is not conclusive at this time, and further efforts to reduce the uncertainties in epidemiological data and dosimetry are being undertaken by the URCRM research group.

A recent investigation of cancer mortality among Hanford workers (*27*) found an increase of ERR with age at exposure. The cohort includes 26,389 workers with mean and median doses of 27.9 and 4.3 mSv, respectively. For ages at exposure under 35 years, a positive but statistically insignificant ERR was found. In the age range from 35 to 54 years a zero or negative risk was obtained, whereas for ages 55+ the risk was large, with an ERR of 3.24 Sv^{-1} (90% CI 0.80; 6.17). The lag time was assumed to be 10 years. The large risk for 55+ years might be due mainly to smoking. A risk analysis of non-lung cancer mortality gave an ERR of 1.73 Sv^{-1} (90% CI −0.77; 4.72). The total cancer risk for all ages was an ERR of 0.28 Sv^{-1} (90% CI −0.30; 1.00). Though the ERR for all solid cancers is lower than in the ETRC, in the observed age dependence and in the value of the ERR for ages at exposure of 55+ years we find an interesting similarity to the patterns seen in the ETRC. An increase of risk for an age at exposure of 55 years could start to show up, assuming a lag time of 10 years, in an increase of risk for an attained age of 65 years, which is exactly what is observed in this work. Furthermore, the value of ERR from the Hanford study (without smoking) agrees very well with our own findings for the exposed individuals whose attained age is 65 years and over.

The results of a 15-country collaborative study of cancer risk among workers in nuclear industry have recently been published (*28*). The analysis included 407,391 nuclear workers with protracted low-dose exposure. The ERR for all cancers excluding leukemia was determined to be 0.97 Sv^{-1} (90% CI 0.27; 1.80). The highest ERRs were found in workers with the highest attained age; for age older than 70 years, the ERR was 1.96 Sv^{-1} (90% CI 0.61; 3.75). Both the central risk value and the increase in risk with attained age agree very well with the findings of this work. Furthermore, an investigation of age at exposure revealed a lower risk for age at exposure before 35 years and a higher risk for ages between 35 and 50 and for ages over 50 (ERR/Sv −1.07, 1.32 and 1.74, respectively).

In the mechanistic interpretation of the TSCE model, the increased sensitivity to radiation with age is due to the significantly larger value of the parameter that describes the increase of the initiation rate per dose rate after the age of 30 years (X_2) than the parameter that describes the increase before the age of 30 (X_1) from Table 2. Given the parameters of the TSCE model, one can see that though an exposure at some age starts to increase the excess risk after the lag time, its main contribution to the risk will only begin to show up 30–40 years after exposure. The step function model of Eq. (4) should be taken as a simplification, and in reality there would be a much smoother transition between younger and older ages. A similar effect was seen in the empirical ERR model where a substantial increase in excess risk was observed in the people exposed after the age of 30 years compared those ones exposed at younger ages, though this effect was not significant. The increase in radiation risk with age at exposure could be explained by a decline in cellular repair mechanisms and immune function with age (*29*). The transition age found in this work of about 30 years for both TSCE models and the ERR model is very close to the higher risk for age at exposure over 35 years found by Cardis *et al.* (*28*). We think that the observations of the relationship between risk and age at exposure or attained age are interesting and deserve future attention.

[2] We thank Linda Walsh for providing us these risk estimates.

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